

Hindered Phenols Category Justification and Testing Rationale

CAS Nos.: 68457-74-9, 61788-44-1, 96-69-5, 85-60-9, 79-96-9, 7786-17-6,
68610-51-5 and 27676-62-6
(+ Chemicals 128-37-0, 2082-79-3 and 6683-19-8 for data purposes)

Rubber and Plastic Additives Panel
American Chemistry Council
December 2001

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List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives Panel of the American Chemistry Council include the following member companies: Bayer Corporation, Ciba Specialty Chemicals Corporation, Crompton Corporation, Flexsys America L.P., The Goodyear Tire & Rubber Company, The Lubrizol Corporation, Noveon, Inc., R.T. Vanderbilt Company, Inc., and UOP, LLC.

Executive Summary

The American Chemistry Council's Rubber and Plastic Additives Panel (RAPA), and its member companies, hereby submit for review and public comment their test plan for the Hindered Phenols category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program.

Hindered phenols are non-staining, non-discoloring, non-migratory additives for natural rubber, synthetic rubber, adhesives, plastics, textile fibers, cable coatings, flooring, and coated paper as well as natural and synthetic oils. Their sole purpose is to prevent or greatly delay the deterioration caused by air oxidation. The hindered phenols are very cost-effective and efficient antioxidants. Usage levels for most applications are typically within the range of 0.5 to 2%. Due to their low volatility and non-migratory nature, many hindered phenol antioxidants are regulated for use by the Food and Drug Administration (FDA) in a number of food-contact applications as an Indirect Food Additive.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted a thorough literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information to fill certain data requirements. It is concluded that there are sufficient data on the members of this category for the purposes of the HPV Program and therefore, no additional testing is recommended.

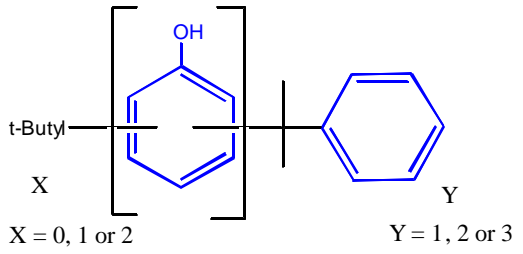
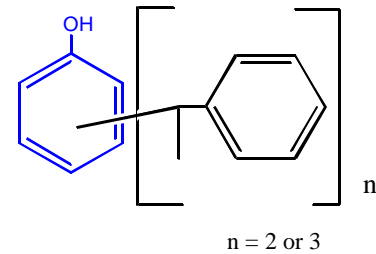
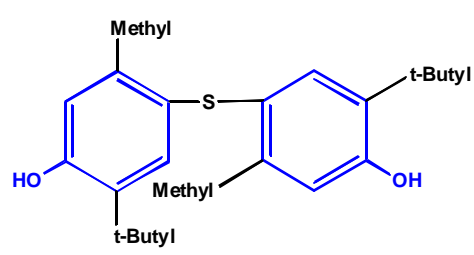
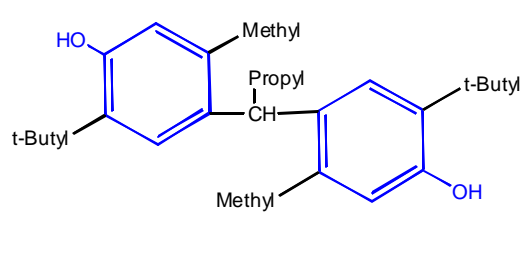
Hindered Phenols Category

As defined by EPA under the HPV Program, a chemical category is “a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity.” The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing with specific consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals.

Relying on several factors specified in EPA’s guidance document on “Development of Chemical Categories in the HPV Challenge Program,”¹ in which use of chemical categories is encouraged, the following related chemicals constitute a chemical category.

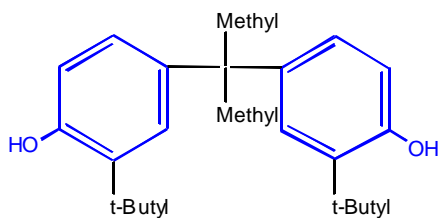
Structural Similarity: The hindered phenols category consists of a group of chemicals in which a molecule of phenol (hydroxybenzene) has relatively large aliphatic and/or aromatic groups positioned adjacent to the hydroxyl group (the 2-, or ortho- position).

Eight substances form the hindered phenols category based on structural similarity:

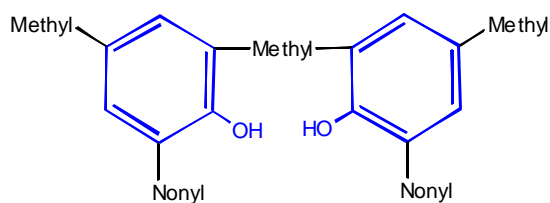
<p><i>Phenol, isobutyleneated methylstyrenated</i> (68457-74-9)</p> 	<p><i>Phenol, styrenated</i> (61788-44-1)</p> 
<p><i>4,4'-Thiobis-6-(t-butyl-m-cresol)</i> (96-69-5)</p> 	<p><i>4,4'-Butylidenebis(6-t-butyl-m-cresol)</i> (85-60-9)</p> 

¹ US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. <http://www.epa.gov/opptintr/chemrtk/categuid.htm>

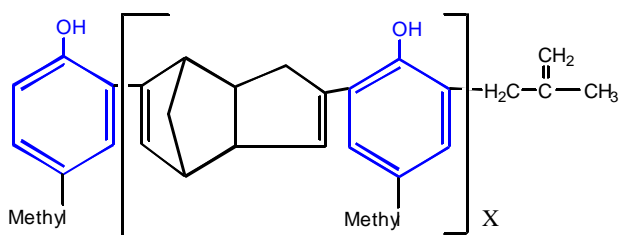
***Phenol, 4,4'-(1-methylethylidene)bis
[2-(1,1-dimethylethyl)]-,
(79-96-9)***



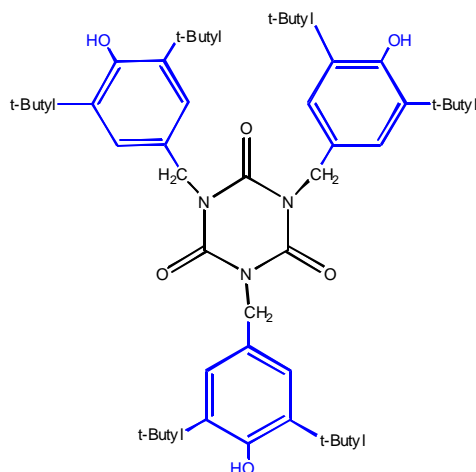
***Phenol, 2,2'-methylenebis(4-methyl-
6-nonyl)
(7786-17-6)***



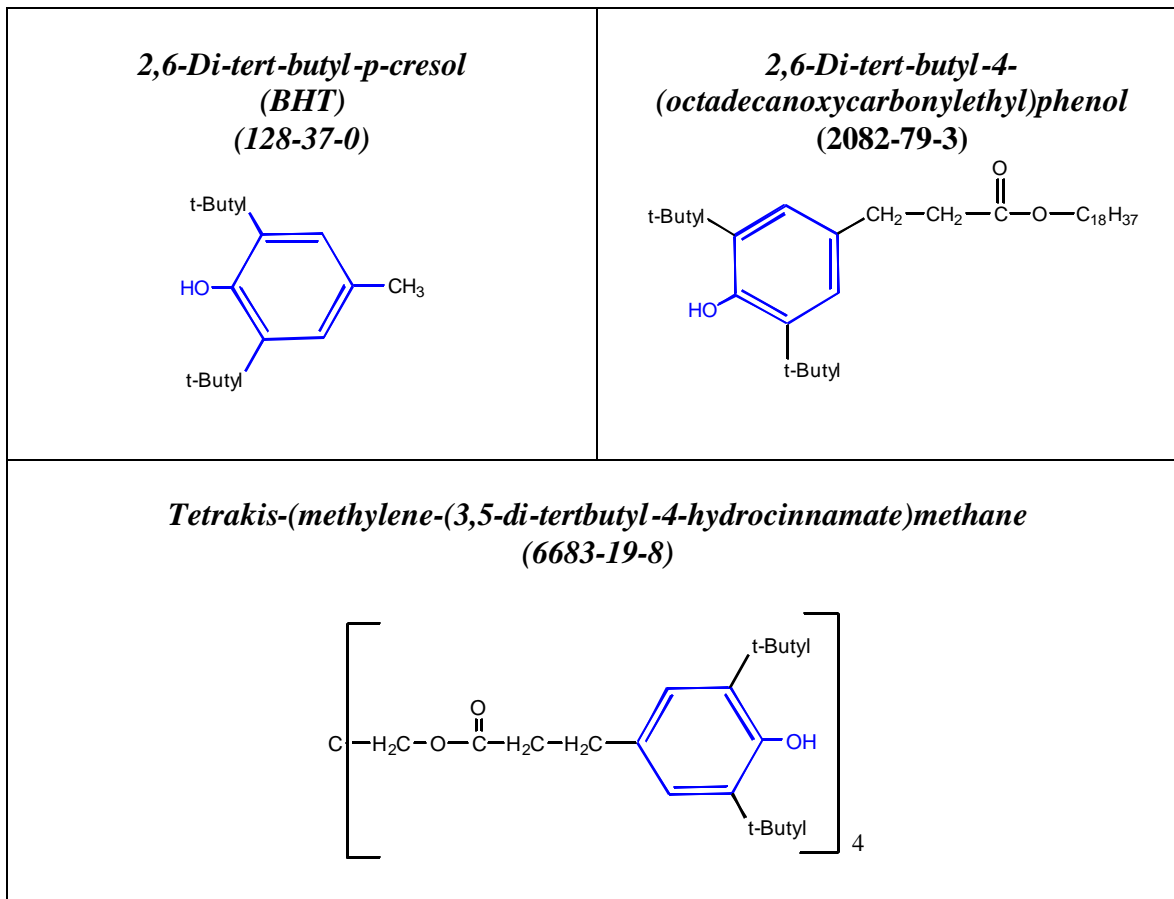
***Phenol, 4-methyl-, reaction products with
dicyclopentadiene and isobutylene
(68610-51-5)***



***1,3,5-tris(3,5-di-tert-butyl-4-
hydroxybenzyl)-1,3,5-triazine-
2,4,6(1H,3H,5H)-trione
(27676-62-6)***



The hindered phenols sponsored in the HPV Program by the RAPA Panel are not a comprehensive list of substances that would fit a hindered phenols category. To better take advantage of the benefits of using a category approach, data for three additional hindered phenols that are not part of the group supported by the RAPA Panel are included in the category justification discussion:



Similarity of Physiochemical Properties: Hindered phenols are either solids or liquids at room temperature. The vapor pressure of these chemicals is low. Generally, the water solubility for the group chemicals is low and the partition coefficients are high.

Fate and Transport Characteristics. Experimental data show that hindered phenols are not readily biodegradable. With one exception, the low water solubility of these chemicals precludes experimentally obtaining hydrolysis data. Model derived photodegradation indicates that these substances photodegrade rapidly. Fugacity modeling shows that, generally, partitioning would be to soil and sediments rather than air or water. Modeling has been done for all of the substances where the model could be applied and bridging can be done to those substances where the model was not suitable. Additional modeling for the members of this category is not necessary for the purposes of the HPV Program.

Toxicological Similarity. Review of existing published and unpublished test data for the

hindered phenols shows that the aquatic and mammalian toxicity among the substances in this category are similar.

Aquatic Toxicology. Hindered phenols have low water solubility and, therefore, low aquatic toxicity. Experimental data are available on acute fish toxicity, acute invertebrate toxicity, and alga toxicity for the majority of chemicals in this category. Data can be bridged to those substances without experimental data. No additional ecotoxicity testing is proposed for the purposes of the HPV Program.

Mammalian Toxicology - Acute. Acute oral and dermal toxicity data are available for all but two of the substances in the group. The data show that acute toxicity of these substances is low. The testing for acute toxicity spans five decades. While the majority of studies may not be to current guidelines, tests done according to recent guidelines and under GLP confirm the conclusions of the earlier testing. No additional acute toxicity testing is proposed for the purposes of the HPV Program.

Mammalian Toxicology - Mutagenicity. Data from bacterial reverse mutation assays and *in vitro* and *in vivo* chromosome aberration studies were reviewed. Adequate bacterial gene mutation assays have been conducted with all of the category chemicals except two. Chromosome aberration studies, *in vitro* and/or *in vivo*, are available for all but three substances. The mutagenicity data span the range of structures and molecular weights and missing data can be bridged from other members of the group. The weight of evidence for mutagenic potential for this category indicates these substances are not mutagenic. The category has been adequately tested for mutagenicity to meet requirements of the HPV Program, therefore, no additional mutagenicity testing is proposed.

Mammalian Toxicology – Repeated Dose Toxicity. Repeated dose toxicity data of approximately three months (90-day, 12- and 13-week) are available for most of the substances in this group. Data on repeated dose toxicity were not identified for three substances. Reliable chronic toxicity/carcinogenicity studies have been done on two of the group members. Adequate data span the range of structures and molecular weights and missing data can be bridged from other members of the group. Sufficient data are available for meeting the requirements of repeated dose toxicity of the hindered phenols for the purposes of the HPV Program.

Mammalian Toxicology - Reproductive and Developmental Toxicity. For the majority of the hindered phenol chemicals some evaluation of effects on reproduction or reproductive organs is available. Multi-generation reproduction studies are available for three of the substances in this group. Evaluation of effects on reproduction for four of the hindered phenols is provided by histopathological data on male and female reproductive organs from the repeated dose toxicity studies. Developmental toxicity data exist for five of the substances included in this group. Available data for reproductive and developmental toxicity span the range of structures and molecular weights and can be bridged to those group

members where data have not been identified. No additional testing is proposed for the purposes of the HPV Program.

Conclusion Based on the data reviewed in this document, the physicochemical and toxicological properties of the proposed hindered phenols category are similar and follow a regular pattern as a result of that structural similarity. Therefore, the EPA's definition of a chemical category has been met for the 11 chemicals in the hindered phenols category, and the panel proposes no additional testing for the purposes of the HPV Program.

Introduction

A provision for the use of structure activity relationships (SAR) to reduce testing needs is included under EPA's HPV Program. Specifically, categories may be formed based on structural similarity, through analogy, or through a combination of category and analogy for use with single chemicals. The benefits of using a category approach are numerous. They include the accelerated release of hazard information to the public (category analysis and testing are proposed to be initiated within the first two years of the HPV Program); a reduction in the number of animals used for testing; and an economic savings as a result of a reduced testing program.

The eight substances that form the hindered phenols category based on structural similarity are:

- phenol, isobutylene-methylstyrene (68457-74-9)
- phenol, styrene (61788-44-1)
- 4,4'-thiobis-6-(*t*-butyl-*m*-cresol) (96-69-5)
- 4,4'-butylidenebis(6-*t*-butyl-*m*-cresol) (85-60-9)
- phenol, 4,4'-(1-methylethylidene)bis[2,(1,1-dimethylethyl)]- (79-96-9)
- phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)
- phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)
- 1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)

The substances identified as hindered phenols committed to by the RAPA Panel are not a comprehensive list of substances that would fit a hindered phenols category. To better take advantage of the benefits of using a category approach, data for three additional hindered phenols that are not part of the group supported by the RAPA Panel are included in the category justification and test plan. Data for these three substances are either publicly available or have been made available to the Panel by a manufacturer. The substances are:

- 2,6-di-*tert*-butyl-*p*-cresol (128-37-0)
- (octadecanoxycarbonyl ether)phenol (2082-79-3)
- tetrakis-(methylene-(3,5-di-*tert*-butyl-4-hydroxycinnamate)methane (6683-19-8)

The development of this category follows current EPA guidelines.

Background Information: Manufacturing and Commercial Applications

Manufacturing

A typical manufacturing process for a hindered phenol antioxidant uses a substituted cresol raw material for the phenolic ring portion of the molecule, and an aldehyde raw material for the bridging or connecting group. The batch reaction takes place in an alcoholic solvent and utilizes an acid catalyst. When the reaction is complete, the batch is quenched with water and decanted. Purification steps may include additional water washes/decants before the product is slurried with a hydrocarbon solvent, vacuum filtered, washed with additional solvent, centrifuged and dried.

Commercial Applications

Hindered phenols are non-staining, non-discoloring, non-migratory additives for natural rubber, synthetic rubber, adhesives, plastics, textile fibers, cable coatings, flooring, and coated paper, as well as natural and synthetic oils. Their purpose is to prevent or greatly delay the deterioration caused by air oxidation. Using a hindered phenol antioxidant greatly extends the useful life of a transparent, translucent, white or light-colored article by preventing the formation of surface cracks, brittleness and yellowing. In oils, a hindered phenol antioxidant functions as a stabilizer, extending the useful life of the lubricating fluid by slowing the natural breakdown process and limiting the buildup of tars and residues. The overall mechanism is similar to that of the antioxidant vitamins A and E in the human body – hindered phenol antioxidants serve as free-radical scavengers.

Hindered phenols are cost-effective and efficient antioxidants. Usage levels for most applications are typically within the range of 0.5 to 2%.

Due to their low toxicity, low volatility and non-migratory nature, many hindered phenol antioxidants are regulated for use by the Food and Drug Administration (FDA) in a number of food-contact applications as an Indirect Food Additive:

175.105	Components of Adhesives 85-60-9, 96-69-5, 7786-17-6, 61788-44-1, 68610-51-5, 27676-62-6
175.125	Pressure-Sensitive Adhesives 68610-51-5
175.300	Resinous and Polymeric Coatings 85-60-9
177.1632	Poly(phenyleneterephthalamide) Resins 85-60-9
177.2600	Rubber Articles – Antioxidants 85-60-9, 96-69-5, 7786-17-6, 61788-44-1, 68610-15-5
178.2010	Antioxidants and/or Stabilizers for Polymers 85-60-9, 96-69-5, 7786-17-6, 68610-51-5, 27676-62-6

NOTE: 2,6-di-tert-butyl-p-cresol (128-37-0) (butylated hydroxytoluene or BHT), the prototype molecule for the hindered phenol antioxidants, is Generally Recognized As

Safe (GRAS) by the Food and Drug Administration, and is approved for use as a Direct Food Additive and preservative for numerous food products.

Shipping/Distribution

Hindered phenol antioxidants are manufactured in North America, Europe and Asia by more than a dozen different companies. They are shipped worldwide for use at manufacturing sites engaged in the production of rubber and plastic articles and mechanical goods, food containers and food handling equipment, industrial oils and lubricants, synthetic fabrics and specialized papers.

Worker/Consumer Exposure

The rubber and plastics additives industry has a long safety record and sophisticated industrial users handle these materials. Exposure of workers handling hindered phenol antioxidants materials is likely to be highest in the area of material packaging rather than from chemical manufacturing. These materials are made as powders, flakes, emulsions and liquids. Product forms that minimize dust generation, coupled with the mechanized materials handling systems of the large industrial users, combine to keep exposures to minimum levels. However, during material packout at the manufacturing site and, to a lesser degree during weigh-up activities at the customer site, there is a potential for skin and inhalation exposure (nuisance dust is the primary route of worker exposure) and also dermal contact with liquid forms.

All known sales of the hindered phenol antioxidants are to industrial users only. There are no known consumer uses for these materials as manufactured, so there are no expected direct-to-consumer sales. Only very small amounts are used in the manufacture of rubber and plastics or as oil additives, and the materials themselves become bound in the polymer matrix during the rubber and plastic curing process. For these reasons, consumer exposure to hindered phenol antioxidants is believed to be minimal. Should exposure occur, the most likely route would be skin contact from rubber and plastic articles, or from skin contact with oils.

Development of the Hindered Phenols Category

EPA has described a stepwise process for developing categories. These steps include:

- Grouping a series of like chemicals, including the definition of criteria for the group.
- Gathering data on physicochemical properties, environmental fate and effects, and health effects for each member of the category.
- Evaluating the data for adequacy.
- Constructing a matrix of available and unavailable data.
- Determining whether there is a correlation among category members and data gathered.

Definition of the Hindered Phenols Category

As defined by EPA under the HPV Program, a chemical category is “a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity.” The similarities should be

based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing.

The substances to be included in this hindered phenols category are:

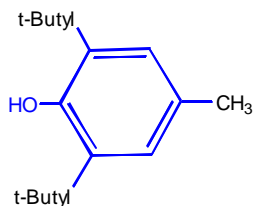
Hindered Phenols

Name	CAS No.
2,6-di-tert-butyl-p-cresol	128-37-0
phenol, isobutylenated methylstyrenated	68457-74-9
phenol, styrenated	61788-44-1
(octadecanoxycarbonyl ether)phenol	2082-79-3
4,4'-thiobis-6-(t-butyl-m-cresol)	96-69-5
4,4'-butylidenebis(6-t-butyl-m-cresol)	85-60-9
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-,	79-96-9
phenol, 2,2'-methylenebis(4-methyl-6-nonyl)	7786-17-6
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene	68610-51-5
tetrakis-(methylene-(3,5-di-tert-butyl-4-hydrocinnamate)methane	6683-19-8
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione	27676-62-6

 = Non-sponsored chemicals; used for data purposes only

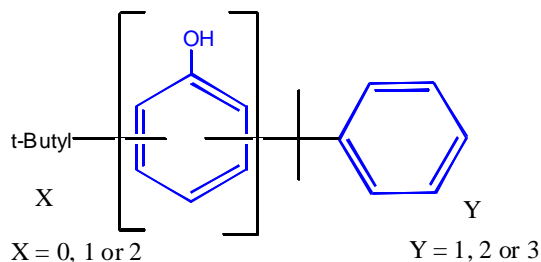
The hindered phenols in this category consist of a group of chemicals in which a molecule of phenol (hydroxybenzene) has multiple substitutions on the aromatic ring with relatively large aliphatic and/or aromatic groups. At least one of the groups is adjacent to the hydroxyl group (the 2-, or ortho- position). Due to the bulky substituent groups, the substances, which may be either room temperature solids or liquids, have limited water solubility, high partition coefficients and are not readily biodegradable.

2,6-di-tert-butyl-p-cresol (128-37-0) (butylated hydroxytoluene or BHT) is hydroxybenzene with aliphatic tertiary butyl groups adjacent to the hydroxyl (OH) group and a methyl group in the 4- or para- position.

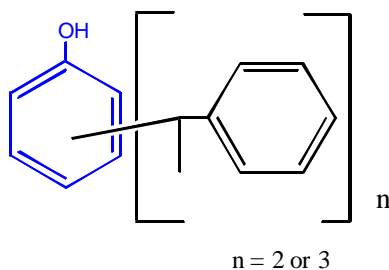


Phenol, isobutylenated methylstyrenated (68457-74-9) is hydroxybenzene with multiple aliphatic and/or aromatic groups on the aromatic ring. At least one group is adjacent to

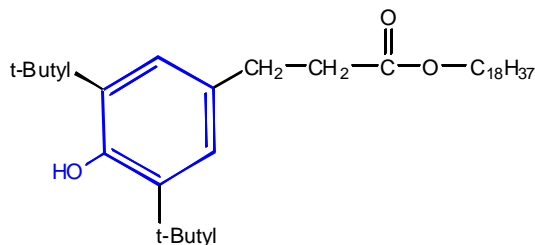
the hydroxyl group, most often the alpha-methyl styrene. Relative to BHT, one, sometimes both, of the tertiary butyl groups has been replaced with an aromatic alpha-methyl styryl group. The methyl group of BHT is replaced by either a tertiary butyl group or an alpha-methyl styrene.



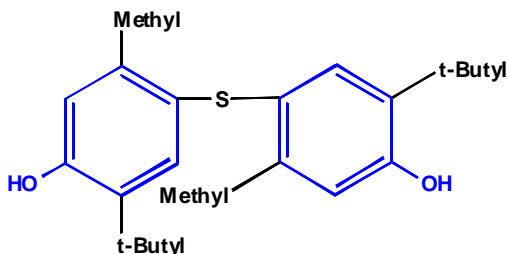
Phenol, styrenated (61788-44-1) has multiple aromatic styryl groups on the hydroxybenzene. Relative to BHT, the butyl groups adjacent to the hydroxyl (OH) group are replaced with styryl groups and the methyl group may either be absent or replaced with a styryl group.



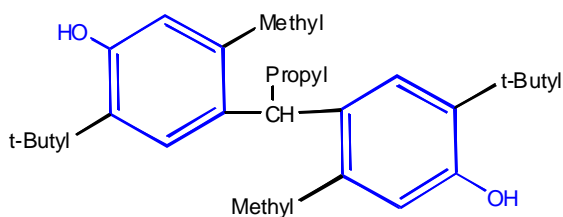
2,6-Di-tert-butyl-4-(octadecanoxycarbonyl)phenol (2082-79-3), like BHT, has aliphatic tertiary butyl groups adjacent to the hydroxyl (OH) group, but the methyl group in the 4-position is replaced with an octadecyl (C18) ester group.



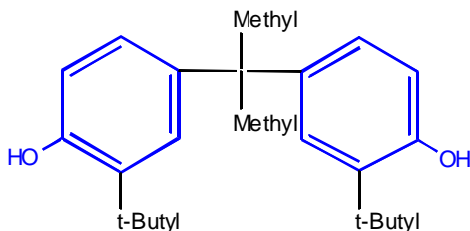
4,4'-Thiobis-6-(*t*-butyl-*m*-cresol) (96-69-5) is two identically substituted hydroxybenzene groups linked by a sulfur bridge. Relative to BHT, one butyl group adjacent to the hydroxyl group (OH) is absent, and a sulfur bridge adjacent to the methyl groups links the two hydroxybenzene groups in this configuration.



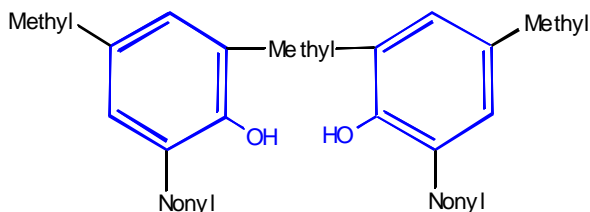
4,4'-Butylidenebis(6-*t*-butyl-*m*-cresol) (85-60-9), like 4,4'-thiobis-6-(*t*-butyl-*m*-cresol) (96-69-5) is two identically substituted hydroxybenzene groups. In each hydroxybenzene ring one of the aliphatic butyl groups adjacent to the hydroxyl (OH) group is absent and an aliphatic isobutyl group adjacent to the methyl groups links the two rings.



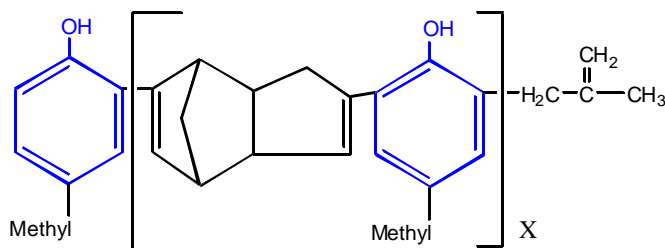
Phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) is two identically substituted hydroxybenzene groups linked by an isopropyl group. Compared to BHT, each hydroxybenzene group lacks one of the tertiary butyl groups adjacent to the hydroxyl group and the isopropyl group linking the two aromatic rings replaces the methyl group.



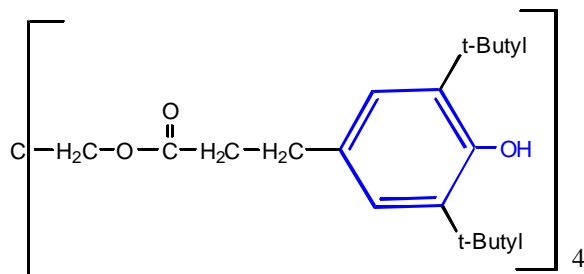
Phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6) is two identically substituted hydroxybenzene groups linked by a methyl group. Compared to BHT, in each hydroxybenzene group, one of the aliphatic butyl groups adjacent to the hydroxyl group (OH) is replaced by an aliphatic nonyl group and the other butyl group is replaced by the methyl group linking the two rings.



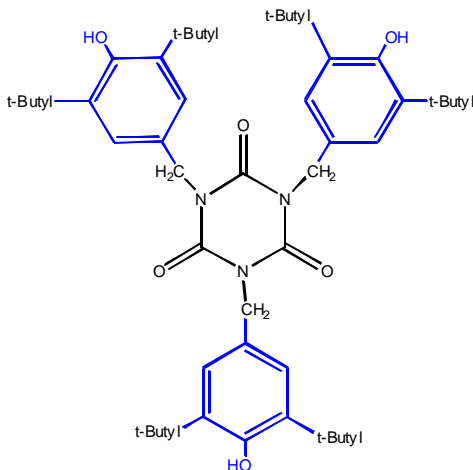
Phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5) is two hydroxybenzene groups which, compared to BHT, have the methyl group in the 4-position, but in place of the butyl group the core hydroxybenzene molecules are linked adjacent to the hydroxyl group by a heterocyclic dicyclopentadiene and/or isobutylene group.



Tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8) is a hindered phenol similar to BHT in that the aliphatic butyl groups remain adjacent to the hydroxyl (OH) group, but the methyl group is absent. In place of the methyl group, four identical molecules in this configuration are linked to a molecule of pentaerythritol by ester groups.



1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6) is a hindered phenol consisting of three BHT molecules connected by a triazine trione.



Matrix of SIDS Endpoints

In order to construct a matrix of SIDS endpoints for the hindered phenols category, the data on physicochemical properties, environmental fate and effects, and health effects for each member of the category must be collected and evaluated for adequacy. The results of these activities are presented in the tables and text below, providing a matrix of available data for the hindered phenols substances.

Correlation within the Hindered Phenols Category

The matrix data patterns for physicochemical properties; environmental fate, ecotoxicity; and health effects have been evaluated for the members of the hindered phenols category. A description of the results of this evaluation follows.

Correlation of Physicochemical Properties

The physicochemical properties of the members of the hindered phenols category are presented in Table 1. These materials may exist as liquids or solids at room temperature. The similarities in the other physicochemical properties of these materials, which are described below, provide justification of this group of chemicals as a category within the HPV Challenge Program. The vapor pressure of these chemicals is low. Generally, the water solubility for the group chemicals is low and the partition coefficient is high.

Experimentally determined melting and/or boiling point data are available for all, but two, of the hindered phenols. Model calculated melting and boiling points are provided for those two and are generally consistent with the experimentally determined values.

Experimentally determined or model calculated vapor pressures are available for all of the group chemicals. Model calculated vapor pressures are consistent with the experimentally determined values.

Experimentally determined water solubility is reported for eight of the group chemicals. These can be used to extrapolate to the other members of the group. Water solubility data for 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9) can be bridged to phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6).

Experimentally determined partition coefficients are available for 2,6-di-tert-butyl-p-cresol (128-37-0); phenol, isobutylenated methylstyrenated (68457-74-9); phenol, styrenated (61788-44-1); tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8); and phenol, 4-methyl-, reaction products with dicyclopentadiene, isobutylene (68610-51-5) and 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6). Model calculated partition coefficients are available for all of the other substances in this category and are consistent with the experimentally determined values.

Experimental or model calculated physiochemical data are available for all chemicals in the category. The model calculated values are consistent with the experimentally determined data. It is concluded that there are adequate data for physicochemical properties for the hindered phenols for the purposes of the HPV Program.

Correlation of Environmental Fate

Data on environmental fate for the substances in the hindered phenols category are presented in Table 2. The hindered phenols are not readily biodegradable, but have rapid photodegradation. As a result of the low water solubility of these chemicals, hydrolysis data are not available, except for one substance. Fugacity modeling indicates that partitioning would generally be to soil and sediments rather than air or water.

Hydrolysis testing is not possible for the hindered phenols because of low water solubility. Data were available only for 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5), indicating that it is not readily hydrolyzed.

Model derived photodegradation half-lives are presented for all of the category substances, except phenol, isobutylenated methylstyrenated (68457-74-9) and phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5). The environmental fate could not be determined with the model for these two substances. The estimate for the photodegradation half-life for phenol, styrenated (61788-44-1) can be bridged to phenol, isobutylenated methylstyrenated (68457-74-9); and for phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5) from tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8).

The hindered phenols are not readily biodegradable. Biodegradation data are available for all but two of the substances. For phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6) data can be bridged from 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9).

The environmental transport model was not applicable to phenol, isobutylene-phenol, isobutylene-methylstyrene (68457-74-9) and phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5). Information for phenol, styrene-phenol (61788-44-1) can be bridged to phenol, isobutylene-methylstyrene (68457-74-9) and tetrakis-(methylene-(3,5-di-tert-butyl-4-hydroxycinnamate)methane (6683-19-8) can be bridged to phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5).

The available data for environmental fate span the range of structures and molecular weights. It is concluded that there are adequate data to evaluate the environmental fate of this group of hindered phenols for the purposes of the HPV Program.

Correlation of Ecotoxicity

The HPV Challenge Program requires an acute aquatic ecotoxicity test in fish, invertebrates, and algae. The substances in the hindered phenol category have low water solubility and this is reflected in low aquatic toxicity. The data for ecotoxicity are summarized in Table 3.

Acute fish toxicity

Fish 96-hour LC50 data are available for all of the chemicals, except phenol, isobutylene-phenol, isobutylene-methylstyrene (68457-74-9), phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6). Due to the similarity in structure it would be expected that the aquatic toxicity of phenol, isobutylene-methylstyrene (68457-74-9), with lower water solubility than phenol, styrene-phenol (61788-44-1), would not have aquatic toxicity greater than phenol, styrene-phenol (61788-44-1). It would be expected that acute fish toxicity of phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6) would be similar to 4,4'-butylidenebis(6-tert-butyl-m-cresol) (85-60-9). It is concluded that there are adequate data to evaluate the acute toxicity to fish for this group of chemicals with limited water solubility for the purposes of the HPV Program.

Acute Invertebrate Toxicity

Acute toxicity data for Daphnia are available for 2,6-di-tert-butyl-p-cresol (128-37-0); (octadecanoxycarbonyl ether)phenol (2082-79-3); 4,4'-thiobis-6-(tert-butyl-m-cresol) (96-69-5); 4,4'-butylidenebis(6-tert-butyl-m-cresol) (85-60-9); phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5); tetrakis-(methylene-(3,5-di-tert-butyl-4-hydroxycinnamate)methane (6683-19-8); and 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6). As with acute fish toxicity, the toxicity in Daphnia is limited by the water solubility of the chemicals. The data for acute invertebrate toxicity span the range of structures and molecular weights. It is concluded that there are adequate data to evaluate the acute toxicity to invertebrates for the purposes of the HPV Program.

Algal Growth Inhibition

Algal growth inhibition tests are available for 2,6-di-tert-butyl-p-cresol (128-37-0); (octadecanoxycarbonylether)phenol (2082-79-3); 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5); 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9); phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5); tetrakis-(methylene-(3,5-di-tert-butyl-4-hydrocinnamate)methane (6683-19-8); and 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6). The data for algal growth inhibition span the range of structures and molecular weights. It is concluded that there are adequate data to evaluate the acute toxicity to invertebrates for the purposes of the HPV Program.

Correlation of Health Effects

Acute Mammalian Toxicity

The acute toxicity of the hindered phenols category is summarized in Table 4. Acute oral and dermal toxicity data are available for all, but two, of the substances in the group. The data show that the acute toxicity of the hindered phenols is low. The testing for acute toxicity spans five decades. While the majority of studies may not be to current guidelines, tests done according to recent guidelines and under GLP confirm the conclusions of the earlier testing. No additional testing is necessary for the purposes of the HPV Program.

Genotoxicity

A summary of the mutagenicity testing for the hindered phenols category are presented in Table 5. The weight of evidence for mutagenic potential for this category indicates these substances are not mutagenic.

Bacterial Gene Mutation Assays. Adequate bacterial gene mutation assays have been conducted with all of the category chemicals, except phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6). All assays, with and without metabolic activation, were negative. It is concluded that this group of substances has been adequately tested for gene mutations for the purposes of the HPV Program.

Chromosome Aberration Studies. Chromosome aberration studies, in vitro and/or in vivo, are available for all but three of the hindered phenols in this group. They are phenol, styrenated (61788-44-1)), phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9), and (p-cresol, 2,2'-methylenebis[6-nonyl] (7786-17-6). With one exception all tests for chromosome aberrations are negative. It is concluded that this group of chemicals has been adequately tested for clastogenic potential for the purposes of the HPV Program.

In Vitro Chromosome Aberration Studies. In vitro chromosome aberration studies are available for 2,6-di-tert-butyl-p-cresol (128-37-0), 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9), and phenol, 4-methyl-, reaction products with dicyclopentadiene, isobutylene (68610-51-5), and 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6). All except 2,6-di-tert-butyl-p-cresol were negative.

In Vivo Chromosome Aberration Studies. In vivo studies evaluating chromosome damage are available for six of the hindered phenols. All in vivo evaluations were negative. Multiple studies have been done with 2,6-di-tert-butyl-p-cresol (128-37-0). Micronucleus tests are available with phenol, isobutyleneated methylstyrenated (68457-74-9); 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5) and 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6). In vivo chromosome aberration studies in Chinese hamsters were negative with (octadecanoxycarbonylether)phenol (2082-79-3) and tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8).

Repeated Dose Toxicity

A summary of the repeated dose toxicity data for the hindered phenols category is presented in Table 6. The summary table is not a comprehensive presentation of all of the repeated dose studies done with the substances in this category. To demonstrate that the substances have been adequately tested for repeated dose toxicity to meet the requirements of the HPV Program, shown in the table are only studies of approximately three months (90-day, 12- and 13-weeks) or longer, unless no data were available and then 28-day studies were used to fill the gap. Three of the category substances are lacking in repeated dose toxicity data. They are (phenol, isobutyleneated methylstyrenated (68457-74-9); phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9); and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6). The data for repeated dose toxicity span the range of structures and molecular weights.

The liver was the target organ in rats for all of the substances with subchronic toxicity data in that species, except 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6) where no target organ was identified. Other target organs were thyroid in phenol, styrenated (61788-44-1); adrenals in phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5); and kidney and mesenteric lymph nodes in 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5). NOAELs in rats ranged from 100 ppm (approximately 5 mg/kg/day) to 10,000 ppm (500 mg/kg/day).

1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6) showed no adverse effects in a 90-day study with dogs at doses up to 10,000 ppm in the diet.

Chronic toxicity/carcinogenicity data are available for 2,6-di-tert-butyl-p-cresol (128-37-0); and 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5). Liver adenomas were reported for 2,6-di-tert-butyl-p-cresol (128-37-0) and a NOAEL was established for the study at 25

mg/kg/day. 4,4'-Thiobis-6-(t-butyl-m-cresol) (96-69-5) was not carcinogenic in rats or mice, but the kidney was identified as a target organ in female rats.

The data for repeated dose toxicity span the range of structures and molecular weights. It is concluded that there are adequate data to evaluate repeated dose toxicity for the purposes of the HPV Program.

Reproductive and Developmental Toxicity

A summary of the reproductive and developmental toxicity data for the hindered phenols category is presented in Table 7.

Reproductive Toxicity. Multi-generation reproduction studies have been conducted with three of the substances in this group 2,6-di-tert-butyl-p-cresol (128-37-0); (octadecanoxycarbonylether)phenol (2082-79-3); and tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8).

Evaluation of effects on reproduction for the hindered phenols is supplemented by histopathological data on male and female reproductive organs in repeated dose studies. These are 90-day studies with 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9); phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5); and 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6). A two-year chronic feeding study provided data for 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5). No adverse effects were noted on reproductive organs.

4,4'-Thiobis-6-(t-butyl-m-cresol) (96-69-5) was also tested in an NTP program for screening reproductive toxicants using a postnatal mouse screening test. Increased maternal mortality and decreased pup survival were reported.

No data for the assessment of reproductive toxicity are available for four of the hindered phenol chemicals: phenol isobutylenated methylstyrenated (68457-74-9); phenol, styrenated (61788-44-1); phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9); and (p-cresol, 2,2'-methylenebis[6-nonyl] (7786-17-6).

The data on the effects of hindered phenols on reproduction and reproductive organs span the range of structures and molecular weights. While not all of the data for reproductive effects are from reproduction studies, microscopic evaluations of reproductive organs along with other short-term tests for reproductive effects provide adequate data to evaluate the effects of these hindered phenols on reproduction for the purposes of the HPV Program.

Developmental Toxicity. Developmental studies have been conducted in rats, rabbits, and/or mice with 2,6-di-tert-butyl-p-cresol (128-37-0); (octadecanoxycarbonylether)phenol (2082-79-3); 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5); phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5); and tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8). The available data span the range of structures and molecular weights and

provide adequate data to evaluate the effects of these hindered phenols on development for the purposes of the HPV Program.

Conclusion

The 11 hindered phenols meet the EPA definition of a chemical category. This group consists of chemicals in which a molecule of phenol (hydroxybenzene) has multiple substitutions on the aromatic ring with relatively large aliphatic and/or aromatic groups. At least one of the groups is adjacent to the hydroxyl group (the 2-, or ortho- position). Due to the bulky substituent groups, the substances have limited water solubility, high partition coefficients and are not readily biodegradable. Therefore, the EPA's definition of a chemical category has been met.

The test plan for the hindered phenols category was developed giving careful consideration to the number of animals that would be required for any tests that are not available for certain members of the category and whether these additional tests would provide useful and relevant information. The test plan is summarized in Table 8. It is concluded that there are sufficient data on the members of this category for the purposes of the HPV Program and therefore, no additional testing is recommended.

Table 1.
Matrix of Available and Adequate Data for the Hindered Phenols Category
Physicochemical Properties

Name (CAS No.)	Molecular Weight	Melting Point °C	Boiling Point °C	Vapor Pressure (mm Hg)	Water Solubility (mg/L)	Partition Coefficient
2,6-di-tert-butyl-p-cresol (128-37-0)	220.36	70	265	0.0225 at 25 °C	0.4 at 20 °C 1.1 at 20 °C	5.1
phenol, isobutylenated methylstyrenated (68457-74-9)	386 (average)		350	0.0018 at 25 °C	0.0287 – 0.375 at 30 °C pH 7.9 - 8	>6.2
phenol, styrenated (61788-44-1)	330 (average)	<0	200 - 250	0.102 at 25 °C (calculated)	59 at 20 °C pH 5.6 – 5.9	>4
(octadecanoxycarbonyl ether)phenol (2082-79-3)	530.9	49 -54	561 (calculated)	4.2 x 10 ⁻¹¹ (calculated)	ND	13.4 (calculated)
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	358.58	156 - 158		6.3 x 10 ⁻⁷ at 70 °C	<0.1 at 25 °C	8.24 (calculated)
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	382.64	210		5.26 x 10 ⁻¹¹ at 25 °C (calculated)	<0.1 at 18 °C	9.09 (calculated)
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	340.51	181 (calculated)	433 (calculated)	1.18 x 10 ⁻⁹ at 25 °C (calculated)	ND	7.46 (calculated)
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	480.78	252 (calculated)	584 (calculated)	6.25 x 10 ⁻¹⁵ at 25 °C (calculated)	ND	13.10 (calculated)
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	750 - 850	118.3		< 2.4 x 10 ⁻⁷ at 25 °C	0.2 at 20 °C	7.17 - 8.17
tetrakis-(methylene-(3,5-di-tert-butyl-4-hydrocinnamate)methane (6683-19-8)	1178	115 - 118	1130 (calculated)	7.1 x 10 ⁻³¹ at 25 °C (calculated)	< 0.1	23
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	784.1	219.5 – 225.5	961 °C (calculated)	5 x 10 ⁻¹⁵ at 25 °C (calculated)	<1 at 25 °C	>6

ND - No data found

 = Non-sponsored chemicals; used for data purposes only

Table 2
Matrix of Available and Adequate Data for the Hindered Phenols Category
Environmental Fate

Name (CAS No.)	Hydrolysis	Photo-degradation (t1/2)	Bio-degradation	Environmental Transport
2,6-di-tert-butyl-p-cresol (128-37-0)	ND	25.2% remained after 8 days 17 hr (EPIWIN)	Aerobic approximately 10% after 56 days; 4.5% after 28 days.	Primarily in air (Mackay, Level I model) Adsorbs to river sediments from water.
phenol, isobutylenated methylstyrenated (68457-74-9)	cbd	cbd (EPIWIN)	Aerobic degradation <1% after 29 days	cbd (EPIWIN)
phenol, styrenated (61788-44-1)	ND	2.2 hr (EPIWIN)	Aerobic degradation 7% after 28 days	Primarily water and soil. (Level III Fugacity Model)
(octadecanoxycarbonyl ether)phenol (2082-79-3)	ND	3 hr (model calculated)	Partially biodegradable Inherently biodegradable	Primarily soil (Level III Fugacity Model)
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	>168 hrs at pH 7 at 23 °C	1 hr (EPIWIN)	Aerobic 11% after 90 days	Primarily soil and sediments. (Level III Fugacity Model)
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	ND	0.6 hr (EPIWIN)	Aerobic 0-5% after 35 days	Primarily soil and sediments. (Level III Fugacity Model)
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	1.3 hr (EPIWIN)	ND	Primarily soil and sediments. (Level III Fugacity Model)
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	1.9 hr (EPIWIN)	ND	Primarily soil and sediments. (Level III Fugacity Model)
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	cbd	cbd (EPIWIN)	Not biodegradable	cbd (EPIWIN)
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydroxyinnamate)methane (6683-19-8)	ND	1.2 hr (model calculated)	Not biodegradable	Primarily soil (Level III Fugacity Model)
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	ND	1.9 hr (EPIWIN)	Not biodegradable	Primarily soil and sediments. (Level III Fugacity Model)

ND - No data found cbd - cannot be determined due to low solubility

cbd (EPIWIN) - cannot be determined by modeling


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Table 3.
Matrix of Available and Adequate Data for the Hindered Phenols Category
Ecotoxicity

Name (CAS No.)	Acute Fish 96-hr LC50 (mg/L)	Acute Invertebrate 48-hr EC50 (mg/L)	Algal Growth Inhibition EC50 (mg/L)
2,6-di-tert-buty-p-cresol (128-37-0)	> 0.57	>.31	0.42
phenol, isobutylenated methylstyrenated (68457-74-9)	ND	ND	ND
phenol, styrenated (61788-44-1)	> 3.2	ND	ND
(octadecanoxycarbonylether)phenol (2082-79-3)	> 100	> 100 (24-hr)	> 30
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	0.13 - 0.16 trout 0.24 - 0.51 bluegill 0.14 - 0.36 minnow	0.70	126
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	> 1000 in trout, blue gill and minnow	16	> 1000
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND	ND
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	>0.2 (limit of solubility)	>0.2 (limit of solubility)	>0.2 (limit of solubility)
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	> 100	> 86 (24-hr)	> 100
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	> 100	> 32	> 100

ND - No data found


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Table 4.
Matrix of Available and Adequate Data for the Hindered Phenols Category
Acute Toxicity

Name (CAS No.)	Acute Oral (mg/kg)	Acute Dermal (mg/kg)
2,6-di-tert-buty-p-cresol (128-37-0)	> 2930	> 2000
phenol, isobutylenated methylstyrenated (68457-74-9)	> 2000	> 2000
phenol, styrenated (61788-44-1)	3550	> 5010
(octadecanoxycarbonyl ether)phenol (2082-79-3)	> 5000	> 2000
4,4'-thiobis-6-(t-butyl- m-cresol) (96-69-5)	4150	>5010
4,4'-butylidenebis(6-t-butyl- m-cresol) (85-60-9)	> 7940	> 7940
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	> 5010	> 5010
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	> 10,250	> 3160
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	> 5000	> 2000

ND - No data found

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Table 5.
Matrix of Available and Adequate Data for the Hindered Phenols Category
Genotoxicity

Name (CAS No.)	Bacterial Gene Mutation	Chromosomal Aberrations	
		In vitro	In vivo
2,6-di-tert-butyl-p-cresol (128-37-0)	negative	positive	negative
phenol, isobutylenated methylstyrenated (68457-74-9)	negative	ND	negative
phenol, styrenated (61788-44-1)	negative	ND	ND
(octadecanoxycarbonylether)phenol (2082-79-3)	negative	ND	negative
4,4'-thiobis-6-(t-butyl- m-cresol) (96-69-5)	negative	ND	negative
4,4'-butylidenebis(6-t-butyl- m-cresol) (85-60-9)	negative	negative	ND
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND	ND
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	negative	negative	ND
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	negative	ND	negative
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	negative	negative	negative

ND - No data found

= Non-sponsored chemicals; used for data purposes only

Table 6.
Matrix of Available and Adequate Data for the Hindered Phenols Category
Repeated dose Toxicity

Name (CAS No.)	Subchronic Toxicity	Chronic Toxicity
2,6-di-tert-buty-p-cresol (128-37-0)	Oral toxicity in rats from 2-gen repro study. F1 gen evaluated at 4 wks and at 6, 11, 16, and 22 mo. NOAEL 25 mg/kg/day	Chronic oral toxicity in rats - 144 wk study. Liver adenomas. NOAEL 25 mg/kg/day
phenol, isobutylated methylstyrenated (68457-74-9)	ND	ND
phenol, styrenated (61788-44-1)	12-Week feeding study in rats - Growth was retarded and liver wts relative to bw. were higher than controls; minimal focal thyroid hyperplasia. NOAEL = 50 mg/kg/day LOAEL = 158 mg/kg/day	ND
(octadecanoxycarbonylether)phenol (2082-79-3)	28-Day gavage in rats - Target organ liver. NOAEL = 30 mg/kg/day	ND
4,4'-thiobis-6-(t-butyl- m-cresol) (96-69-5)	<p>13-Week feeding study in rats - Higher ALP and ALT; lower hematocrit and HB conc and RBC; histopath findings in liver (hypertrophy and hyperplasia), kidney (renal cortical tubule effects), and mesenteric lymph nodes (increased size and number of macrophages). NOEL = 500 ppm LOEL = 1000 ppm</p> <p>13-Week feeding study in mice - Higher ALP and ALT; effects on hematocrit, HB conc and RBC; histopath findings in liver (hypertrophy and hyperplasia) and mesenteric lymph nodes (increased size and number of macrophages). NOEL = 250 ppm LOEL = 500 ppm</p>	<p>Two-year feeding study in rats - Higher AP, ALT and sorbitol dehydrogenase; lower hematocrit, HB conc, and RBC counts; histopath findings in liver; increased severity of nephropathy in females. Not carcinogenic. NOEL = 500 ppm LOEL = 1000 ppm</p> <p>Two-year feeding study in mice - Higher AP and bilirubin ; lower hematocrit, HB conc, and RBC counts Not carcinogenic. LOEL = 250 ppm</p>

ND - no data found


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Table 6. (continued)
Matrix of Available and Adequate Data for the Hindered Phenols Category
Repeated dose Toxicity

Name (CAS No.)	Subchronic Toxicity	Chronic Toxicity
4,4'-butylidenebis(6-t-butyl- m-cresol) (85-60-9)	90-Day feeding study in rats - Increased liver weights, effects on SGOT and SGPT. Microscopic changes in liver and lymph nodes. NOAEL = 100 ppm LOAEL = 500 ppm	ND
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	90-Day feeding study in rats - Increased liver wts and increased adrenal wts (females only) at 1500 ppm and higher. NOAEL = 500 ppm (25 mg/kg/day)	ND
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	13-Week feeding study in dogs - No adverse effects, NOEL = 10,000 ppm (highest dose tested)	ND
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	3-Month feeding study in rats - Increased food consumption in males and elevated platelet count in females. For males NOEL = 3,000 ppm (201mg/kg/day) For females NOEL = 800 ppm (50.1 mg/kg/day) 90-Day feeding study in rats - No adverse effects, NOEL = 10,000 ppm (highest dose tested) 90-Day oral feeding study in dogs - No adverse effects, NOEL = 10,000 ppm (highest dose tested)	ND

ND - No data found


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Table 7.
Matrix of Available and Adequate Data for the Hindered Phenols Category
Reproductive and Developmental Toxicity

Name (CAS No.)	Reproductive	Developmental
2,6-di-tert-butyl-p-cresol (128-37-0)	2-Generation in rats at 25 to 500 mg/kg/day (F0) and 25 and 250 mg/kg/day (F1) 2-Generation in mice - Increased wt of pups at birth and during lactation. NOEL not established. LOEL=22.5 mg/kg/day	Mice by gavage - NOAEL for maternal tox = 240 mg/kg/day and NOAEL for terata >= 800 mg/kg/day. Rat teratology, not teratogenic from two publications from Japan
phenol, isobutylated methylstyrenated (68457-74-9)	ND	ND
phenol, styrenated (61788-44-1)	ND	ND
(octadecanoxycarbonylether)phenol (2082-79-3)	2-Generation in rats - NOAEL (F0) = 1500 ppm; LOAEL (F1 and F2) = 500 ppm	In rats - Not teratogenic. NOAEL for maternal tox = 150 mg/kg/day. In mice - Not teratogenic. NOAEL for maternal tox > 1000 mg/kg/day.
4,4'-thiobis-6-(t-butyl- m-cresol) (96-69-5)	Histopathology of sex organs from chronic toxicity study in rats. No adverse effects. NTP postnatal mouse screening test. One dose = 485 mg/kg/day. Increased maternal mortality, decreased pup survival	Developmental in rabbits - Maternal NOEL = 0.2 mg/kg/day. Effects on fetuses only at maternally toxic doses.

ND - No data found



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Table 7 (continued).
Matrix of Available and Adequate Data for the Hindered Phenols Category
Reproductive and Developmental Toxicity

Name (CAS No.)	Reproductive	Developmental
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	Histopathology of sex organs from 90-day repeated dose study in rats. No adverse effects.	ND
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	Histopathology of sex organs from 90-day repeated dose study in rats. No adverse effects.	In rats - Not teratogenic; increased incidence of common fetal skeletal variations. NOAEL for maternal tox = 1000 mg/kg/day. BMD at ED ₀₅ for fetal variations = 740 mg/kg/day
tetrakis-(methylene-(3,5-di-tert-butyl-4-hydrocinamate)methane (6683-19-8)	2-Generation in rats at 1000 to 10,000 ppm. NOAEL (F0, F1, F2) = 10,000 ppm	In rats - Not teratogenic. NOAEL for maternal tox > 1,000 mg/kg/day. In mice - Not teratogenic. NOAEL for maternal tox > 1000 mg/kg/day.
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	Histopathology of sex organs from 3-month repeated dose study in rats. No adverse effects.	ND

ND - No data found

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Legend for Table 8

Symbol	Description
A	Endpoint requirement fulfilled with adequate existing data
NA	Not applicable due to physical/chemical properties
C	Endpoint requirement fulfilled based on calculated data
R	Endpoint requirement fulfilled using category approach, SAR

Table 8.
Hindered Phenols Category Test Plan

Physicochemical Properties

Name (CAS No.)	Melting Point	Boiling Point	Vapor Pressure	Water Solubility	Partition Coefficient
2,6-di-tert-buty-p-cresol (128-37-0)	A	A	A	A	A
phenol, isobutylenated methylstyrenated (68457-74-9)	NA	A	A	A	A
phenol, styrenated (61788-44-1)	A	A	C	A	A
(octadecanoxycarbonylether)phenol (2082-79-3)	A	C	C	R	C
4,4'-thiobis-6-(t-butyl- m-cresol) (96-69-5)	A	NA	A	A	C
4,4'-butylidenebis(6-t-butyl- m-cresol) (85-60-9)	A	NA	C	A	C
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	C	C	C	R	C
phenol, 2,2'-methylenebis(4- methyl-6-nonyl) (7786-17-6)	C	C	C	R	C
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	A	NA	A	A	A
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	A	C	C	A	A
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	A	C	C	A	A


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Table 8 (continued).
Hindered Phenols Category Test Plan

Environmental Fate

Name (CAS No.)	Hydrolysis	Photo-degradation	Bio-degradation	Environmental Transport
2,6-di-tert-butyl-p-cresol (128-37-0)	NA	A	A	A
phenol, isobutylenated methylstyrenated (68457-74-9)	NA	R	A	R
phenol, styrenated (61788-44-1)	NA	C	A	C
(octadecanoxycarbonylether)phenol (2082-79-3)	NA	C	A	C
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	A	C	A	C
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	NA	C	A	C
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	NA	C	R	C
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	NA	C	R	C
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	NA	R	A	R
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	NA	C	A	C
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	NA	C	A	C

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**Table 8 (continued).
Hindered Phenols Category Test Plan
Ecotoxicity**

Name (CAS No.)	Acute Fish	Acute Invertebrate	Algal Growth Inhibition
2,6-di-tert-buty-p-cresol (128-37-0)	A	A	A
phenol, isobutylenated methylstyrenated (68457-74-9)	R	R	R
phenol, styrenated (61788-44-1)	A	R	R
(octadecanoxycarbonylether)phenol (2082-79-3)	A	A	A
4,4'-thiobis-6-(t-butyl- m-cresol) (96-69-5)	A	A	A
4,4'-butylidenebis(6-t-butyl- m-cresol) (85-60-9)	A	A	A
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	R	R
phenol, 2,2'-methylenebis(4- methyl-6-nonyl) (7786-17-6)	R	R	R
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	A	A	A
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	A	A	A
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	A	A	A

Acute Toxicity

Name (CAS No.)	Acute Oral	Acute Dermal
2,6-di-tert-buty-p-cresol (128-37-0)	A	A
phenol, isobutylenated methylstyrenated (68457-74-9)	A	A
phenol, styrenated (61788-44-1)	A	A
(octadecanoxycarbonylether)phenol (2082-79-3)	A	A
4,4'-thiobis-6-(t-butyl- m-cresol) (96-69-5)	A	A
4,4'-butylidenebis(6-t-butyl- m-cresol) (85-60-9)	A	A
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	R
phenol, 2,2'-methylenebis(4- methyl-6-nonyl) (7786-17-6)	R	R
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	A	A
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	A	A
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	A	A


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Table 8 (continued).
Hindered Phenols Category Test Plan

Genotoxicity

Name (CAS No.)	Bacterial Gene Mutation	Chromosomal Aberrations	
		In vitro	In vivo
2,6-di-tert-butyl-p-cresol (128-37-0)	A	A	A
phenol, isobutylenated methylstyrenated (68457-74-9)	A	R	A
phenol, styrenated (61788-44-1)	A	R	R
(octadecanoxycarbonylether)phenol (2082-79-3)	A	R	A
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	A	R	A
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	A	A	R
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	R	R
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	R	R	R
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	A	A	R
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	A	R	A
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	A	A	A

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Table 8 (continued).
Hindered Phenols Category Test Plan

Repeated dose Toxicity

Name (CAS No.)	Subchronic Toxicity	Chronic Toxicity
2,6-di-tert-butyl-p-cresol (128-37-0)	A	A
phenol, isobutylenated methylstyrenated (68457-74-9)	R	
phenol, styrenated (61788-44-1)	A	
(octadecanoxycarbonylether)phenol (2082-79-3)	A	
4,4'-thiobis-6-(t-butyl- m-cresol) (96-69-5)	A	A
4,4'-butylidenebis(6-t-butyl- m-cresol) (85-60-9)	A	
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	
phenol, 2,2'-methylenebis(4- methyl-6-nonyl) (7786-17-6)	R	
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	A	
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	A	
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	A	

Reproductive and Developmental Toxicity

Name (CAS No.)	Reproductive	Developmental
2,6-di-tert-butyl-p-cresol (128-37-0)	A	A
phenol, isobutylenated methylstyrenated (68457-74-9)	R	R
phenol, styrenated (61788-44-1)	R	R
(octadecanoxycarbonylether)phenol (2082-79-3)	A	A
4,4'-thiobis-6-(t-butyl- m-cresol) (96-69-5)	A	A
4,4'-butylidenebis(6-t-butyl- m-cresol) (85-60-9)	A	R
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	R
phenol, 2,2'-methylenebis(4- methyl-6-nonyl) (7786-17-6)	R	R
phenol, 4-methyl-, reaction products with dicyclopentadiene and isobutylene (68610-51-5)	A	A
tetrakis-(methylene-(3,5-di-tertbutyl-4-hydrocinnamate)methane (6683-19-8)	A	A
1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (27676-62-6)	A	R

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